Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Type 3 hypersensitivity in COVID-19 vasculitis

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) is an ongoing public health emergency and new knowledge about its immunopathogenic mechanisms is deemed necessary in the attempt to reduce the death burden, globally. For the first time in worldwide literature, we provide scientific evidence that in COVID-19 vasculitis a life-threatening escalation from type 2 T-helper immune response (*humoral immunity*) to type 3 hypersensitivity (*immune complex disease*) takes place. The subsequent deposition of immune complexes inside the vascular walls is supposed to induce a severe inflammatory state and a cytokine release syndrome, whose interleukin-6 is the key myokine, from the smooth muscle cells of blood vessels.

Coronavirus Disease 2019 (COVID-19) is an ongoing public health emergency around the world and the acquisition of new knowledge about its immunopathogenesis is required in the attempt to reduce the death burden, globally. As well known, naïve T-helper cells (T_h0) can detect pathogens never encountered before, like the specific case of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the etiological agent responsible for the disease, able to infect the human cells via angiotensin-converting enzyme 2 receptors [1]. Classically, on the basis of the novel infectious agent, T_h0 polarize the immune response into type 1 T-helper (T_h1), the default response in immunocompetent subjects to intracellular or phagocytosable pathogens (e.g. viruses, bacteria, protozoa, fungi) and mediated by macrophages and T-cytotoxic (T_c) cells (*cell-mediated immunity*), or into type 2T-helper (T_h2), typically directed against extracellular non-phagocytosable pathogens, for instance helminths, and whose main effectors are eosinophils, basophils and mastocytes, as well as B cells (*humoral immunity*) [2]. The ultimate goal of humoral immunity is to produce opsonising antibodies and to generate memory cells able to promptly counteract the pathogen in the future, if necessary [3]. During our researches on COVID-19, we have disclosed that, for reasons still unclear and maybe related to the viral load or to T_h1 and T_c breakdown, the immune system is forced to mount a T_h2 response against SARS-CoV-2 in patients requiring intensive care, rather than a T_h1 response, which would keep the infection under control by means of macrophages and T_c cells [4]. According to Gell and Coombs classification, type 3 hypersensitivity takes place when an excess or slight excess of soluble antigens lead to the accumulation of immune complexes, not enough cleared from the circulation by the innate immune system [5]. These antigen-antibody complexes precipitate inside the tissues, in particular blood vessels, inducing a severe inflammatory state by the action of complement anaphylatoxins (C3a and C5a), which in turn stimulate the release of histamine from mast cells and the recruitment of phagocytes, *in primis* neutrophils, the main responsible for the tissue damage [5]. On histopathology, the result of this process inside the walls of blood vessels is depicted by an acute necrotizing vasculitis with neutrophilic infiltration, karyorrhexis and fibrinoid necrosis, the so called «leukocytoclastic vasculitis» (LCV), also reported in the English medical literature by the term «hypersensitivity vasculitis» [6]; platelet aggregation correlates with hypercoagulability and thrombosis, disorders described in course of COVID-19, too [7]. The just mentioned fibrinoid necrosis represents a specific pattern of tissue injury, which occurs once antigen-antibody complexes are deposited in the walls of blood vessels along with fibrin and complement anaphylatoxins; therefore, it can be considered a diagnostic clue of immune-mediated vasculitides from type 3 hypersensitivity [8]. LCV is preceded by a viral infection, such as hepatitis B, hepatitis C and HIV, in a relevant percentage of cases [6]. The onset time of type 3 hypersensitivity varies from days to weeks depending on the presence or not of memory cells against the precipitating antigen; clinical features emerge approximately 10 days after initial antigenic challenge [8]. During the Severe Acute Respiratory Syndrome (SARS) outbreak in 2002–2003, caused by SARS-CoV-2 predecessor (SARS-CoV), it was observed that the acute respiratory distress syndrome, one the most serious complications of the disease, significantly overlapped with antiviral immunoglobulin G (IgG) seroconversion [9]; besides, it was found that patients who developed more quickly the anti-spike neutralizing antibody showed a higher risk of dying from the disease [10]. Translating our current findings on COVID-19, these alarming data can be now explained for the first time in worldwide literature by a life-threatening escalation from T_h2 immune response to type 3 hypersensitivity with the subsequent deposition of antigen-antibody complexes, particularly inside the walls of blood vessels, to such an extent as to generate a systemic vasculitis in the context of an immune complex disease (Fig. 1). This event is accompanied by complement C3 activation, which is positioned upstream of the thrombo-inflammatory complement cascade in COVID-19; therefore, to prevent C3 activation into C3a anaphylatoxin through specific inhibitors, like compstatin-based AMY-101, can provide effective therapeutic results [11]. Preexisting endothelial dysfunctions due to atherosclerosis could worsen the deposition process in elderly and middle-aged patients [12]; since the smooth muscle cells in tunica media of blood vessels are able to produce interleukin-6 (IL-6) [13], a key myokine of inflammation and of the cytokine release syndrome, their inflammatory involvement can justify well the described «cytokine storm» in COVID-19 critical patients, a dramatic phenomenon remained not fully elucidated up to date.

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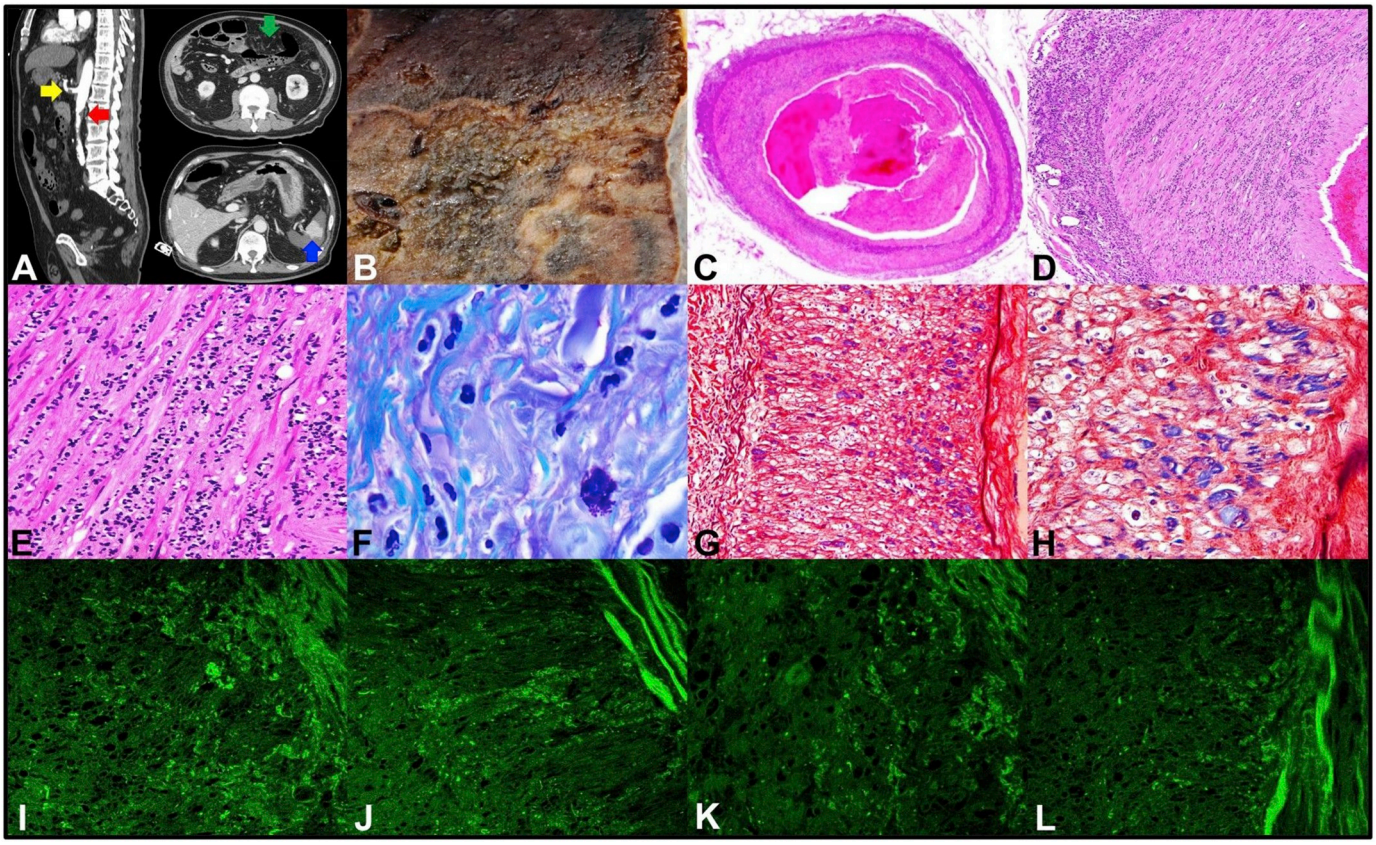

Fig. 1. Ileal and splenic infarctions in a 72-year-old Italian male patient affected by COVID-19 and submitted to rescue surgery after 18 days from SARS-CoV-2 molecular detection through nasopharyngeal swab [IL-6 sequential dosages by serum immune assays: from 154.03 ρg/ml - day 1 to 2656.46 ρg/ml - day 18]: on sagittal abdomen computed tomography (CT) scan with contrast medium, an aortic thrombus (A, red arrow) and one at the celiac tripod (A, yellow arrow) are clearly visible, while on axial abdomen CT scans a large ischemic intestinal loop shows pneumatosis intestinalis (A, green arrow) and only a central portion of healthy spleen (A, blue arrow) remains vascularized by the splenic artery; grossly, the transition zone between the upper residual spleen parenchyma and the lower discolored infarcted area is captured (B); on histopathology, the splenic artery appears thrombosed and involved by vasculitis (C, hematoxylin & eosin, 2.5× objective); at higher magnification (D, hematoxylin & eosin, 10× objective), the inflammation is arranged around (periarteritis) and inside (panarteritis) the vascular wall; in the cytological details, neutrophils and karyorrhexis are well noticeable, a classical histological picture for LCV (E, hematoxylin & eosin, 60× objective), while Toluidine blue stain highlights the purple granules of a mast cell in the degranulation phase close to polymorphonuclear neutrophils (F, 100× objective); phosphotungstic acid hematoxylin reveals blue spots of fibrinoid necrosis in the full thickness of the splenic artery wall (G, 40× objective), more concentrated just below the internal elastic membrane in the innermost part of tunica media (H, 100× objective); immunofluorescence confirms the presence of green-brightened immune complexes, mainly consisting of IgG (I, anti-human polyclonal IgG/FITC, 100× objective), but also of IgM (J, anti-human polyclonal IgM/FITC, 100× objective) and IgA (K, anti-human polyclonal IgA/FITC, 100× objective), together with C3 complement deposits (L, anti-human polyclonal C3 complement/FITC, 100× objective). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Declaration of Competing Interest

None of the authors has any financial conflict of interest to disclose.

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